Effect of Yogurt as a Deglutition Aid on the Disintegration and Dissolution of Oral Tablets

Taisuke Matsuo (tmatsuo@iwate-med.ac.jp)
Iwate Medical University

Yoshiyuki Tabata
Fujicco Co., Ltd

Hina Sasaki
Iwate Medical University

Yuki Yoshida
Iwate Medical University

Yayoi Gotoh
Fujicco Co., Ltd

Toshio Suzuki
Fujicco Co., Ltd

Michiko Obara
Teikyo Heisei University

Yasuyuki Sadzuka
Iwate Medical University

Takashi Tomita
Teikyo Heisei University

Research Article

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Abstract

With an aging society, the number of people with dysphagia has increased. Patients with dysphagia not only find it difficult to eat and drink, but also to take oral medications. Swallowing aid foods, such as deglutition aid jellies and food thickeners are often used to help patients take oral medications. However, the inappropriate use of swallowing aids can decrease the pharmacological activity of the medications. Yogurt is nutritious and easy for patients with dysphagia to eat. Although yogurt is sometimes used to help take medications, its influence on them is poorly understood. In this study, we compared the physical properties and the effects of yogurt on disintegration and dissolution profiles of various oral tablets with those of deglutition aid jelly and xanthan gum-based food thickener. Yogurt and food thickener were found to extend the disintegration time of several tablets, but it remained within a few minutes. Although dissolution of magnesium oxide tablets decreased by 6%, 14%, and 25% after immersion in deglutition aid jelly, food thickener, and yogurt, respectively at 15 min, this decrease reduced with time. Rheological measurements showed that yogurt and food thickeners exhibited a weak gel structure and therefore had better fluidity than deglutition aid jelly. The viscosity and adhesiveness of yogurt were higher than those of food thickener, which delayed tablet disintegration and reduced the dissolution rate. However, these effects were not large. Yogurt may be a useful swallowing aid for patients with dysphagia taking oral medications.

Introduction

Aging and disease can make swallowing difficult for many elderly patients. This increases the risk of accidental aspiration of food and drinks [1–4]. It can also make it difficult for patients to take oral medications [4, 5]. Patients with dysphagia use food thickeners to increase the viscosity of liquids, and deglutition aid jellies to convert solids into a gelatinous form to aid the intake of medications [6]. However, these swallowing aids can interfere with the disintegration of dosage forms and the dissolution of the drugs in them [7–11]. Immersing tablets in food thickeners for a long time can delay or inhibit their disintegration [10]. Therefore, it is important to minimize the immersion times (within 1 min) to avoid problems with disintegration [10]. The immersion of voglibose orally disintegrating (OD) tablets in deglutition aid jelly for 10 min has been reported to reduce its pharmacological activity [11]. Research on the effects of food thickeners and deglutition aid jellies on the administration of oral medications has increased our understanding of the area.

Yogurt has moderate viscosity and hardness, making it a suitable training meal for patients with dysphagia. The use of yogurt to help take medications was recommended in the Japanese Dysphagia Diet 2013 by the Japanese Society of Dysphagia Rehabilitation dysphagia diet committee [12]. In clinical practice, yogurt is used to help patients with dysphagia take medications [3]. Its condition is used as an index of hardness for foods [6]. However, the effects of yogurt on the disintegration and dissolution of oral medications are poorly understood.
The properties of yogurts vary depending on the lactic acid bacteria used in their manufacture, and affect the degree of swallowing required. Some lactic acid of bacteria synthesize exopolysaccharides, which affect the viscosity, hardness, and adhesiveness of yogurt. *Lactococcus lactis* subsp. *cremoris* FC (*L. cremoris* FC) is a strain of lactic acid bacteria isolated from fermented milk from the Caucasus region [13]. *L. cremoris* FC produce exopolysaccharides, which affect the texture and stability of the yogurt [13–15]. It has been reported that yogurt manufactured using *L. cremoris* FC decreases the rate of laryngeal invasion and aspiration in patients with dysphagia, compared to that manufactured using other types of lactic acid bacteria [16]. We hypothesized that yogurt manufactured using *L. cremoris* FC could be used as an aid for the administration of oral medication. In this study, we investigated the effects of yogurt on the disintegration and dissolution of magnesium oxide tablets, used by patients in care facilities, in comparison with xanthan-based food thickener and deglutition aid jelly. The effects of these swallowing aids on other oral medications, film-coated tablets, sugar-coated tablets, enteric-coated tablets, and OD tablets were also evaluated. The physical properties, rheology, viscosity, and adhesiveness of the swallowing aids were also compared.

**Materials And Methods**

**2.1. Materials**

The choice of medications used in this study were based on the results of a questionnaire survey conducted in care facilities [17]. Details of the medications used in this study are shown in Table 1. Deglutition aid jelly, xanthan gum-based food thickener, and yogurt made with *L. cremoris* FC was purchased from Ryukakusan Co. Ltd. (Swallowing aid jelly; Tokyo, Japan), Clinico Co. (Tsururinko Quickly, 3.0 g/pack; Tokyo, Japan), and Fujicco Co. Ltd. (Caspian Sea Yogurt; Hyogo, Japan), respectively.

**2.2. Preparation of food thickener**

This method for the preparation of the xanthan gum-based food thickener has been previously described [10]. In brief, xanthan gum-based food thickener (3.0 g) was added to 100 mL of soft water (natural mineral water from the South Japanese Alps; Suntory Beverage & Food Limited, Japan) and mixed. The prepared food thickener was used 2 min after mixing.

**2.3. Disintegration test**

The disintegration test was performed as described in the Japanese Pharmacopeia (17th Edition) [18]. This method has been previously described in the literature [10, 19]. The tablets were immersed in each deglutition aid for 1 min, and then transferred to a basket of the disintegration testing apparatus (NT-40HS, Toyama Sangyo Co., Ltd., Japan). Approximately 0.5–1.0 g of the swallowing aids were left attached to tablets. The test was carried out using the first fluid (pH 1.2) and the second fluid (pH 6.8). The enteric-coated tablets were tested in both fluids, while the others were tested only at pH 1.2. The disintegration time was defined as the time when the contents of the tablets were completely released from the baskets. The maximum test time was 2 h. Each experiment was performed using nine tablets.
2.4. Dissolution test for magnesium oxide tablets

The dissolution test was performed using the paddle apparatus, as described in the Japanese Pharmacopeia (17th Edition) [20]. This method has previously been described in the literature [19]. Magnesium oxide tablets were pre-treated with the swallowing aid foods as described in Sect. 2.3. Magnesium oxide content in the dissolution medium was measured by chelate titration using ethylenediaminetetraacetic acid (EDTA).

1 mL of 0.05 mol/L EDTA = 2.015 mg of magnesium oxide.

2.5. Rheological measurements

The yogurt was tested at 10°C, and the other samples were tested at 20°C. Dynamic viscoelasticity measurement were obtained using a controlled stress rheometer MCR-102 (Anton Paar, Austria) equipped with corn plates (50 mm diameter, angle 1°). The temperature of the measuring cell was maintained with a Peltier system P-PTD200 (Anton Paar, Austria). Samples were placed between the rheometer plates. To determine the linear viscoelastic region, strain-dependent measurements were made from 0.01 to 10% strain at a frequency of 1 Hz. As a result, 0.1% strain was adopted as the measurement condition. To evaluate the viscoelastic properties of the samples, frequency-dependent measurements were made between 0.1 Hz and 10 Hz at 1% strain, and the storage moduli ($G'$), loss moduli ($G''$), and loss tangent ($\tan \delta = G''/G'$) were determined.

2.6. Viscosity measurements

The viscosities of yogurt (10°C) and food thickener (20°C) were evaluated. Viscosity was measured using a Brookfield viscometer (DV-I Prime, Brookfield Engineering, MA, USA) at 12 rpm. A No. 64 spindle was used to measure the viscosity of yogurt and a No. 63 spindle was used for evaluation of the food thickener. The samples were poured into plastic containers or glass beakers (height: 830 mm; diameter: 1150 mm) and the spindles were immersed in them. The spindles were rotated for 2 min, and the viscosity was measured.

2.7. Adhesiveness

The evaluation of adhesiveness has previously been described in the literature [10]. Briefly, the deglutition aids (10.0 g) were added to a 100 mL polyvinylpyrrolidone (PVP) or glass beaker. The beaker was reversed for 1 min and adhesiveness was defined as the residue rate in the beaker.

2.8. Statistical analysis

Data are presented as the mean ± standard deviation. Statistical analyses were performed using t-test or one-way analysis of variance with post hoc test (Dunnett's or Tukey-Kramer method). Differences were considered statistically significant if $p < 0.05$.

Results
3. 1. Effects of yogurt on the disintegration and dissolution of magnesium oxide tablets

The disintegration times of magnesium oxide tablets immersed in yogurt were compared with those with deglutition aid jelly and food thickener (Fig. 1). Magmitt® tablets, magnesium oxide tablets “MOCHIDA,” “KENEI”, and “Yoshida,” disintegrated within 4–11 s, even after immersion in deglutition aid jelly and food thickener. The disintegration times of the tablets immersed in yogurt reached a maximum of 70 s. The magnesium oxide tablet “Mylan” disintegrated in approximately 30 s without immersion in deglutition aids. When the tablets were immersed in deglutition aid jelly, food thickener, and yogurt, their disintegration times were approximately 1 min, 2 min, and 40 s, respectively. Parts of foods were left attached to tablets after disintegration, which may affect the dissolution. The dissolution rate of the Magmitt® tablets was measured (Fig. 2). The dissolution rates of magnesium oxide without food at 15, 30, 60, and 120 min were found to be 84%, 90%, 95%, and 98%, respectively. The rates of dissolution after immersion in yogurt, food thickener, and deglutition aid jelly were found to be 60%, 70%, and 78%, respectively at 15 min. However, the dissolution rates of all the samples were over 90% at 120 min, and were similar to those of the non-immersed tablets.

3.2. Effects of yogurt on the disintegration of other oral tablets

Three furosemide tablets (two uncoated and one film-coated tablet), four amlodipine tablets (one film-coated and three OD tablets), an aspirin tablet (an enteric-coated tablet), and a sodium valproate tablet (a sugar-coated tablet) were evaluated (Figs. 3 and 4). Immersion of the tablets in deglutition aid jelly was not found to prolong the disintegration time of any of the tablets compared with the non-immersed tablets. Yogurt and food thickeners were found to delay the disintegration of Lasix® (furosemide) tablets and three OD tablets. On the other hand, the film-coated tablets showed rapid disintegration after immersion in all the deglutition aids. The enteric-coated aspirin tablets did not disintegrate in the first test medium (pH 1.2) in any of the cases, but disintegrated in approximately 10 min in the second test medium (pH 6.8). The disintegration of the sugar-coated Valerin® tablets was not affected by immersion in the deglutition aids.

3.3. Comparison of physical properties of the deglutition aids

Figure 5 shows the change in the dynamic viscoelasticities as a function of frequency for different gels. The tan δ values of the deglutition aid jelly, food thickener, and yogurt were found to be approximately 0.1, 0.3, and 0.3, respectively (Fig. 5a). Although they all exhibited gel-like behavior, the strength of the food thickener and yogurt were lower than that of the deglutition aid jelly. Yogurt had a higher storage modulus G’ and loss modulus G” than the food thickener (Fig. 5b, c). The viscosities of the yogurt and food thickener were found to be 18221 mPa·s and 5106 mPa·s, respectively (Fig. 6a). The adhesiveness
of the yogurt and food thickener were 81% and 54%, respectively in the glass beaker, and 91% and 49%, respectively in the PVP beaker (Fig. 6b, c).

**Discussion**

Yogurt is thought to be an easy-to-eat food for patients with dysphagia because of its appropriate viscosity and hardness. Yogurt is rich in nutrients such as proteins, minerals, and vitamins, and it had been reported to prevent sarcopenia [21, 22]. If yogurt could be used as an aid to take oral medications, it is expected that medication adherence would improve in patients who usually consume yogurt.

It has been reported that yogurt made using the *L. cremoris* FC strain is better at preventing aspiration compared to those made using other strains of lactic acid bacteria [16]. The effects of *L. cremoris* FC-containing yogurt on the disintegration of magnesium oxide tablets were low. Drug release from the tablets was found to be lower at 15 min, but was similar to that of non-immersed tablets or those immersed in jelly and food thickener at 120 min, during the dissolution experiment. The gastric retention times of medicines are generally within 120 min [23]. Yogurt was found to delay the disintegration of some rapidly disintegrating tablets (some magnesium oxide tablets and OD tablets). This tendency was similar to that of food thickeners, but the disintegration times tended to be slightly longer with yogurt than with the food thickener. Deglutition aid jelly, on the other hand, did not cause a delay in disintegration.

Viscoelastic measurements are widely used for the evaluation of physical properties of materials and foods, including food thickeners [24, 25]. The gel-like behavior of the deglutition aid jelly was found to be stronger than that of the two other swallowing aids. Deglutition aids jelly is a mixture of solid and liquid. The solids of the jelly attached themselves to the tablets, allowing water to easily invade the voids of jelly solids around the tablets. The yogurt and food thickeners exhibited weaker gel-like behavior than the deglutition aid jelly. The results showed that the high fluidity of the yogurt and food thickener tended to extend the disintegration time of some of the tablets immersed in them. Additionally, the $G'$, $G''$, viscosity, and adhesiveness of the yogurt were higher than those of the food thickener. As a result, the detachment of yogurt from the tablets might be more difficult than that of the food thickener. The swallowing aid foods attached to the tablets could not immediately detach from the tablets after disintegration. Therefore, yogurt decreased the dissolution of magnesium oxide tablets in the early part of the experiment. Moreover, casein, which is found in yogurt, aggregates under acidic conditions [26]. This might have caused the delay in disintegration and the reduction in the rate of dissolution in the acidic medium.

It is important to establish the safety of oral medications when taken with yogurt, and to verify the effects of yogurts on various medications, both *in vitro* and *in vivo*. The pharmaceutical activities of bisphosphonates, tetracyclines, and quinolones are reduced by calcium in milk. Therefore, these medications cannot be given with yogurt. Furthermore, the effects of yogurt on the taste of the medications were not evaluated in this study. It is important to evaluate these factors in order to ensure
medication adherence. It is crucial for pharmacists to confirm the dietary habits and the methods for taking medications with patients with dysphagia so that the optimal swallowing aids can be recommended.

In conclusion, this study demonstrated that yogurt manufactured using *L. cremoris* FC did not significantly affect the disintegration or dissolution profiles of magnesium oxide tablets or the other oral tablets evaluated. Like deglutition aid jelly and food thickeners, yogurt may be useful in helping patients with dysphagia take oral medications.

**Declarations**

**Conflicts of Interest**

Taisuke Matsuo was funded by Fujicco Co., Ltd.. Yoshiyuki Tabata, Yayoi Gotoh, and Toshio Suzuki are employees of Fujicco Co., Ltd. The other authors declare no potential conflicts of interest.

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**Author contributions**

Taisuke Matsuo designed the study, conducted experiments, analyzed and interpreted the data, and wrote the manuscript. Yoshiyuki Tabata conducted rheological and viscosity measurements. Hina Sasaki and Yuki Yoshida conducted the dissolution experiments. Data interpretation was performed by Yayoi Gotoh, Toshio Suzuki, Michiko Obara, Yasuyuki Sadzuka, and Takashi Tomita. All authors read and approved the final manuscript.

**References**


Tables
Figures

Figure 1

Disintegration time of magnesium oxide tablets Five types of magnesium oxide tablets: (a) Magmitt®, (b) magnesium oxide tablets “MOCHIDA,” (c) “KENEI,” (d) “Yoshida,” (e) “Mylan,” were immersed in swallowing aids for 1 min. All experiments were performed in an aqueous medium of pH 1.2 (n = 9). The numbers in the figure represent the following: 1, not immersed; 2, immersed in yogurt; 3, immersed with deglutition aid jelly; 4, immersed in food thickener. *P < 0.05, **P < 0.01, and ***P < 0.001 represent significant differences (compared with non-immersed tablets, Dunnett’s test).
Figure 2

Dissolution rate of Magmitt® tablets after immersion in swallowing aid foods. The dissolution rates of the Magmitt® tablets were measured at 15, 30, 60, and 120 min by chelate titration (n = 3). The symbols in the figure indicate: × not immersed, ● yogurt, ▲ deglutition aid jelly, △ food thickener. aP < 0.05, a'P < 0.01, a''P < 0.001 (vs non-immersed tablets) bP < 0.05, and b'P < 0.01 (vs tablets immersed in deglutition aid jelly) represent significant differences (compared with all samples tested at the same time points, Turkey Kramer test).
Figure 3

Disintegration time of furosemide and amlodipine tablets: The (a) Lasix®, (b) furosemide “TAKEDA TEVA,” (c) “NP,” (d) Norvasc® OD, (e) amlodine® OD, (f) amlodipine OD “SAWAI,” and (g) amlodipine 2.5 mg “SAWAI,” tablets were immersed in swallowing aid foods for 1 min before conducting the disintegration time experiments. All experiments were performed in aqueous medium of pH 1.2 (n = 9). The numbers in the figure represent the following: 1, not immersed; 2, immersed in yogurt; 3, immersed with deglutition aid jelly; 4, immersed in food thickener. **P < 0.01 and ***P < 0.001 represent significant differences (compared with non-immersed tablets, Dunnett’s test).
Figure 4

Disintegration time of aspirin and sodium valproate tablets. The tablets were immersed in swallowing aid foods for 1 min. The disintegration of Bayaspirin tablets was evaluated at (a) pH 1.2 and at (b) pH 6.8 (n = 9). (c) The disintegration of sodium valproate tablets was evaluated at pH 1.2 (n = 9). The numbers in the figure represent the following: 1, not immersed; 2, immersed in yogurt; 3, immersed with deglutition aid jelly; 4, immersed in food thickener. **P < 0.01 and ***P < 0.001 represent significant differences (compared with non-immersed tablets, Dunnett’s test).
Figure 5

Frequency-dependent changes in viscoelastic properties. Viscoelastic properties of all the samples were examined by dynamic viscoelasticity measurements (n = 3). (a) tan δ, (b) frequency-dependent storage moduli, $G'$, and (c) loss moduli, $G''$. The symbols in the figure indicate: ● yogurt, □ food thickener, □ deglutition aid jelly.
Evaluation of viscosity and adhesiveness Viscosity and adhesiveness between yogurt and the food thickener were compared (n = 3). (a) Viscosity. (b) Adhesiveness in glass beakers. (c) Adhesiveness in polyvinylpyrrolidone (PVP) beakers. 1, yogurt; 2, food thickener. **P < 0.01 and ***P < 0.001 represent significant differences (t-test).

**Figure 6**

**Supplementary Files**

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- Table1210517.xlsx